DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021073/S-043, 044
NDA 021842/S-014, 015
NDA 022024/S-008, 007
NDA 021925/S-010, 011

SUPPLEMENT APPROVALS

Takeda Global Research & Development Center, Inc.
Attention: Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Lee:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 7, 2011, received July 8, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- ACTOS (pioglitazone hydrochloride) Tablets (sNDA 21-073/S-043),
- ACTOPLUS MET (pioglitazone hydrochloride and metformin hydrochloride) fixed-dose combination Tablets (sNDA 21-842/S-014),
- ACTOPLUS MET XR (pioglitazone hydrochloride and metformin hydrochloride extended-release) fixed-dose combination Tablets (sNDA 22-024/S-008), and
- DUETACT (pioglitazone hydrochloride and glimepiride) fixed-dose combination Tablets (sNDA 21-925/S-010).

Please also refer to your sNDAs dated and received July 8, 2011 for ACTOS (sNDA 21-073/S-044), ACTOPLUS MET (sNDA 21-842/S-015), ACTOPLUS MET XR (sNDA 22-024/S-007), and DUETACT (sNDA 21-925/S-011).

We acknowledge receipt of your amendments dated August 1 and 3, 2011, for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT, and your risk evaluation and mitigation strategy (REMS) assessments submitted on March 7, 2011, for ACTOS and DUETACT, and on November 4, 2010, for ACTOPLUS MET and ACTOPLUS MET XR.

We also refer to our letter dated June 9, 2011, notifying you of new safety information that we believe should be included in the labeling for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT under Section 505(o)(4) of the FDCA, notifying you that you must submit a proposed REMS modification under Section 505-1, and notifying you of a requirement for a postmarketing study under Section 505(o)(3). The new safety information pertains to a dose- and duration-dependent increase in the risk of bladder cancer in subjects exposed to pioglitazone hydrochloride compared to subjects never exposed to pioglitazone hydrochloride.

Supplemental new drug applications (sNDA 21-073/S-044, sNDA 21-842/S-015, sNDA 22-024/S-007, and sNDA 21-925/S-011) provide for revisions to the labeling for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT, respectively. The agreed upon changes to the language included in our June 9, 2011, letter are as follows (additions are noted by underline and deletions are noted by ~~strikethrough)~~.

For ACTOS:

On the Highlights page, under **WARNINGS AND PRECAUTIONS**:

Bladder cancer: Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data ~~indicate~~ further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer (5.5)

In the Full Prescribing Information, under **WARNINGS AND PRECAUTIONS, 5.5 Urinary Bladder Tumors:**

A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

In the Full Prescribing Information, under **PATIENT COUNSELING INFORMATION, Instructions:**

Tell patients to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms ~~of blood in the urine,~~ such as dysuria or urinary urgency that develop or increase during treatment ~~urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are the possible side effects of ACTOS? ACTOS may cause serious side effects including":**

- **bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOS. You should not take ACTOS if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
    - ~~you see~~ blood or a red color in your urine.
    - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
    - ~~you have pain in your back or lower abdomen~~
    - pain while you urinate

For ACTOPLUS MET:

Under **PRECAUTIONS, General:** ***Pioglitazone hydrochloride:***

A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

Under **Information for Patients:**

Patients should be told to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment ~~of blood in the urine, urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are the possible side effects of ACTOPLUS MET? ACTOPLUS MET may cause serious side effects including":**

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOPLUS MET. You should not take ACTOPLUS MET if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
    - ~~you see~~ blood or a red color in your urine.
    - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
    - ~~you have pain in your back or lower abdomen~~
    - pain while you urinate

~~In studies of pioglitazone (one of the medicines in ACTOPLUS MET), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone.~~

For ACTOPLUS MET XR:

Under **PRECAUTIONS, General:** ***Pioglitazone:***

A five-year interim report of an ongoing 10-year observational cohort study found a non-significant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

Under **Information for Patients:**

Patients should be told to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment ~~of blood in the urine, urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are the possible side effects of ACTOPLUS MET XR? ACTOPLUS MET XR may cause serious side effects including":**

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOPLUS MET XR. You should not take ACTOPLUS MET XR if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
    - ~~you see~~ blood or a red color in your urine.
    - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
    - ~~you have pain in your back or lower abdomen~~
    - pain while you urinate

~~In studies of pioglitazone (one of the medicines in ACTOPLUS MET XR), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone.~~

For DUETACT:

Under **PRECAUTIONS, General:** ***Pioglitazone hydrochloride:***

A five-year interim report of an ongoing 10-year observational cohort study found a non-significant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

Under **Information for Patients:**

Patients should be told to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment ~~of blood in the urine, urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are other possible side effects of DUETACT? DUETACT can cause other serious side effects including":**

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take DUETACT. You should not take DUETACT if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
    - ~~you see~~ blood or a red color in your urine.
    - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
    - ~~you have pain in your back or lower abdomen~~
    - pain while you urinate

~~In studies of pioglitazone (one of the medicines in DUETACT), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone.~~

Supplemental new drug applications (sNDA 21-073/S-043, sNDA 21-842/S-014, (sNDA 22-024/S-008, and sNDA 21-925/S-010) provide for proposed REMS modifications consisting of revisions to the Medication Guides and timetables for submission of assessments of the REMS for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT, respectively.

We have completed our review of these supplemental applications, as amended. They are **approved**, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (texts for the package inserts and Medication Guides), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, provide a highlighted or marked-up copies that shows all changes, as well as clean Microsoft Word versions. The marked-up copies should provide appropriate annotations, including supplement numbers and annual report dates.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since ACTOS was approved on July 15, 1999, ACTOPLUS MET was approved on August 29, 2005, ACTOPLUS MET XR was approved on May 12, 2009, and DUETACT was approved on July 28, 2006, we have become aware of a 5-year interim report of your epidemiological study entitled, "Cohort Study of Pioglitazone and Bladder Cancer in Patients with Diabetes," which showed a dose- and duration-dependent increase in the risk of bladder cancer in subjects exposed to pioglitazone hydrochloride compared to subjects never exposed to pioglitazone hydrochloride. We considered this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of bladder cancer.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1783-1 Continuation and modification of your ten-year epidemiological study assessing whether treatment with pioglitazone hydrochloride is associated with an increased risk of bladder cancer in men and women with diabetes.

The timetable you submitted on July 29, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Amendment Submission:	December 16, 2011
4th Interim Report Submission:	June 30, 2012
Study Completion:	December 31, 2012
Final Report Submission:	December 31, 2013

Submit the protocol to your IND 33729, with a cross-reference letter to your NDA for ACTOS. Submit the final report to the NDA for ACTOS. Prominently identify each submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for ACTOS was originally approved on September 9, 2009, and modified on February 3, 2011. The REMS for ACTOPLUS MET was originally approved on September 14, 2009, and modified on October 21, 2009. The REMS for ACTOPLUS MET XR was originally approved on May 12, 2009, and modified on December 22, 2010. The REMS for DUETACT was originally approved on September 9, 2009. These REMS consist of a Medication Guide and a timetable for submission of assessments of these REMS. Your proposed modification to these REMS consists of revised Medication Guides to include information about the risk of bladder cancer, and revised timetables for submission of assessments of these REMS.

Your proposed modified REMS, submitted on July 7, 2011, received on July 8, 2011, and appended to this letter, are **approved**.

There are no changes to the REMS assessment plan described in our original REMS approval letters for these products.

We remind you that assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered.

With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in these approved REMS, you must submit a REMS assessment and may propose a modification to these approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submissions as appropriate:

NDA 021073/ NDA 021842/NDA 022024/NDA 021925 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021073/ NDA 021842/NDA 022024/NDA 021925
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021073/ NDA 021842/NDA 022024/NDA 021925
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package inserts, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug products must be promptly revised to be consistent with the labeling changes approved in these supplements, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
If you have any questions, call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
08/04/2011